Sequential transarterial chemoembolisation and stereotactic body radiotherapy followed by immunotherapy as conversion therapy for patients with locally advanced, unresectable hepatocellular carcinoma (START-FIT): a single-arm, phase 2 trial

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Summary

Background The synergy between locoregional therapies and immune checkpoint inhibitors has not been investigated as conversion therapy for unresectable hepatocellular carcinoma. We aimed to investigate the activity of sequential transarterial chemoembolisation (TACE) and stereotactic body radiotherapy followed by avelumab (an anti-PD-L1 drug) for locally advanced, unresectable hepatocellular carcinoma.

Methods START-FIT was a single-arm, phase 2 trial in patients with locally advanced hepatocellular carcinoma who were not suitable for curative treatment, conducted in two hospitals in Hong Kong and one in Shenzhen, China. Eligible patients were those aged 18 years or older with an Eastern Cooperative Oncology Group performance status 0–1, Child–Pugh liver function score A5 to B7, tumour size of at least 5 cm, a maximum of three tumour lesions, and adequate hepatic, renal, and bone marrow function. Participants received TACE on day 1, followed by stereotactic body radiotherapy (27·5–40·0 Gy in five fractions) at day 28. Avelumab (10 mg/kg) was administered 14 days following stereotactic body radiotherapy and every 2 weeks thereafter. The primary endpoint was the proportion of patients deemed amenable to curative treatment, defined as those who had a sustained complete or partial treatment response for at least 2 months and if curative treatment could be performed (ie, resection, radiofrequency ablation, or transplantation), analysed by intention to treat. Safety was also analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov (NCT03817736) and has been completed.

Findings Between March 18, 2019, and Jan 27, 2021, 33 patients (32 [97%] men and one [3%] woman) were enrolled. The median sum of the largest diameters of lesions was 15·1 cm (IQR 8·3–14·9). 21 (64%) patients had macrovascular invasion (hepatic vein [n=13], branched portal vein [n=3], or both [n=5]). Median follow-up was 17·2 months (IQR 7·8–25·8). 18 (55%) patients were deemed amenable to curative treatment: four (12%) of 33 patients had curative treatment (resection [n=2] or radiofrequency ablation [n=2]), and 14 (42%) had a radiological complete response and opted for close surveillance. 11 (33%) of 33 patients had treatment-related adverse events that were grade 3 or worse. The most common treatment-related grade 3 or worse adverse event was transient increase in alanine aminotransferase or aspartate aminotransferase (five [15%]) after TACE. Five (15%) patients developed immune-related adverse events of grade 3 or worse (three had hepatitis, two had dermatitis).

Interpretation To our knowledge, this is the first prospective trial using the combination of immunotherapy and locoregional treatment as conversion therapy for locally advanced unresectable hepatocellular carcinoma, with promising results. Future randomised trials with larger cohorts of patients are warranted.

Funding Merck.

Lancet Gastroenterol Hepatol 2023; 8: 169–78

Published Online December 15, 2022 https://doi.org/10.1016/S2468-1253(22)00339-9

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Introduction

Hepatocellular carcinoma is the sixth most common cancer globally and the third leading cause of cancer-related mortality.[1] Transarterial chemoembolisation (TACE) is the most widely adopted therapy for patients with unresectable, liver-limited hepatocellular carcinoma. However, TACE was associated with low response rates (roughly 30%) in patients with large (>5 cm) or multinodular hepatocellular carcinoma.[2,3] In the presence of vascular invasion, systemic therapy is the standard of care, yet the response rates were modest, ranging between 5% and 40%.[4–6] Importantly, the use of either TACE or systemic therapy only modestly affected the ability to downstage locally

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Research in context

Evidence before this study

Immune checkpoint inhibitors can result in modest and durable responses in patients with hepatocellular carcinoma. Although the combination of stereotactic body radiotherapy and immune checkpoint inhibitors is expected to be synergistic, their efficacy and safety have not been prospectively explored in patients with hepatocellular carcinoma. We searched PubMed for studies published in English from Jan 1, 2010, to Dec 31, 2021, with the following terms: "HCC", "SBRT", and "immunotherapy". Our group previously showed clinical activity using a multimodality approach. In addition, our group provided preliminary evidence to support the safety and efficacy of stereotactic body radiotherapy followed by nivolumab when compared with transarterial chemoembolisation (TACE) in patients with bulky unresectable hepatocellular carcinoma.

Added value of this study

The START-FIT trial is the first to report the sequential combination of TACE, stereotactic body radiotherapy, and avelumab in patients with locally advanced unresectable hepatocellular carcinoma. It yielded promising rates of conversion (55%) and complete response (42%). The treatment combination did not detect any new safety concerns.

Implications of all the available evidence

Our results showed that the START-FIT combination is a promising conversion therapy for patients with locally advanced, unresectable hepatocellular carcinoma. The encouraging results from our proposed treatment regimen provide a potential new strategy to expand the application of immune checkpoint inhibitors, radiotherapy, and surgery in patients with locally advanced, unresectable hepatocellular carcinoma. Further clinical studies are needed to evaluate the efficacy of this innovative multimodality treatment approach in Barcelona Clinic Liver Cancer stage B and stage C tumours without extrahepatic spread.

advanced, unresectable hepatocellular carcinoma for curative surgery. To date, there is no established conversion treatment regimen.

Stereotactic body radiotherapy is a promising local therapy associated with impressive tumour response in patients with locally advanced hepatocellular carcinoma.[7] Notably, local response rates were enhanced when combined with TACE.[8,9] Our group showed that stereotactic body radiotherapy, combined with a single course of TACE, conferred substantially better antitumour response and survival benefits than repeated TACE, with similar toxicities.[10] However, out-of-field disease progression remains a substantial drawback to locoregional therapy alone, which provides the rationale for combining TACE and stereotactic body radiotherapy with systemic therapy. Data suggested that locoregional therapy could prime the immune system and modulate the tumour microenvironment, enhancing the response to immune checkpoint inhibitors.[11,12] Clinical trial data supported the rationale to harness the enhanced immune response following locoregional therapy.[13] Furthermore, our pilot data showed that the addition of anti-PD-1 therapy to stereotactic body radiotherapy provided durable control outside of the radiation field with a complete response rate of 50%.[14,15]

Hence, a triple combination of sequential TACE and stereotactic body radiotherapy followed by immune checkpoint inhibitor appeared to be the next logical treatment approach. In this phase 2 clinical study (START-FIT), we aimed to evaluate the safety and activity of the triple combination as conversion therapy in patients with locally advanced unresectable hepatocellular carcinoma.

Methods

Study design and participants

START-FIT was a single-arm, multicentre, investigator-initiated phase 2 trial that investigated the activity and safety of sequential TACE, stereotactic body radiotherapy, and avelumab (an anti-PD-L1 drug) in patients with locally advanced hepatocellular carcinoma, and was conducted at Queen Mary Hospital (Pokfulam, Hong Kong Special Administrative Region, China), Tuen Mun Hospital (Tuen Mun, Hong Kong Special Administrative Region, China), and University of Hong Kong-Shenzhen Hospital (Shenzhen, China). Patients aged 18 years or older with unresectable hepatocellular carcinoma without lymph node or extrahepatic metastases were eligible. Tumours were classified as unresectable after a multidisciplinary team review because either: (1) R0 resection was not feasible; (2) remnant liver volume was less than 30% in patients who did not have cirrhosis or 40% in patients with cirrhosis, or the results of an indocyanine green test were higher than 15%; (3) patients had Barcelona Clinic Liver Cancer (BCLC) stage B and beyond Up-to-7 criteria; or (4) patients had BCLC stage C. Other major inclusion criteria included Eastern Cooperative Oncology Group performance status 0–1; Child–Pugh liver function score A5 to B7; tumour size of at least 5 cm; a maximum of three tumour lesions; and adequate hepatic, renal, and bone marrow functions. Previous curative treatment (eg, resection, radiofrequency ablation, percutaneous ethanol injection) was allowed. Tumours with branched portal vein (VP1 to VP3) or hepatic vein invasion (VV1 to VV2) were allowed. Patients with distant metastasis or tumours with main portal vein invasion (VP4) or inferior vena cava (VV3) were excluded. Patients with severe comorbidities (eg, symptomatic

congestive heart failure, unstable angina, and uncontrolled hypertension) or an estimated life expectancy of less than 3 months were excluded. Patients who received any previous systemic therapy, TACE, radiotherapy to the liver, selective internal radiation, or those with liver volume minus the gross tumour volume of 700 mL or less were also excluded. A comprehensive list of eligibility criteria can be found in the appendix (pp 1–2). All patients provided written informed consent, and the institutional review board committee approved the protocol (institutional review board number: UW 18-541). The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice standards.

Procedures

All patients underwent a single treatment of conventional TACE within 28 days of study enrolment. Conventional TACE was performed by supra-selective cannulation of all the branches supplying the tumour. The emulsion was prepared by mixing iodised oil with cisplatin (1 mg/mL) in a 1:1 ratio. A maximum of 60 mL of emulsion was injected. Preparation of the emulsion was followed by embolisation with gelfoam (gelatin granules) pellets of 1 mm diameter mixed with 40 mg of gentamicin. At 28 days (plus or minus 3 days) after the completion of TACE, stereotactic body radiotherapy was delivered to all lesions. Patients were immobilised via a vacuum foam bag (Vac-LokTM; MEDTEC, IA, USA) and active breathing control to reduce liver motion. Imaging was performed on the inhale breath-hold contrast CT. Gross tumour volume was defined as a tumour focus that was visualised by contrast imaging. The clinical target volume was defined as gross tumour volume with expansion to include the area stained with iodised oil. The individualised planning target volume margins were formulated to compensate for respiratory motion and setup errors. Cone beam CT was acquired on board before each treatment. A radiation dose of 27·5–40·0 Gy in five fractions delivered daily was allowed per protocol. The prescription isodose encompassed 95% of the planning target volume. The final dose was determined such that a maximum tumouricidal dose could be delivered to tumours while respecting the tolerance dose of the organ at risk (appendix p 3). The radiotherapy toxicity was assessed by CTCAE; version 4.01.

Patients received the first dose of intravenous avelumab (10 mg/kg) 14 days (plus or minus 3 days) after the completion of stereotactic body radiotherapy. Avelumab was then given every 2 weeks until the development of grade 3 or worse immune-related adverse events, disease progression, or withdrawal of consent. If the tumour was deemed amenable to surgical intervention, avelumab was also stopped. Dose reduction was not allowed. Dose interruption was permitted up to a maximum of 12 weeks. There was no requirement for the minimum treatment duration of avelumab.

All patients underwent baseline contrast-enhanced MRI of the liver and CT of the thorax. Treatment response evaluation was assessed with MRI after cycle 4, cycle 8, and cycle 12 of avelumab and every 12 weeks thereafter (plus or minus 7 days). Radiological imaging was reported using the modified Response Evaluation Criteria in Solid Tumours (mRECIST). A CT of the thorax was done every 26 weeks or at the time of radiological or clinical evidence of disease progression according to mRECIST criteria. All patients were discussed in a multidisciplinary team board meeting that consisted of surgeons specialising in liver transplantation and liver surgery, clinical oncologists, interventional radiologists, and diagnostic radiologists. This meeting was held once every 2 weeks to decide resectability and treatment failure. All patients underwent complete tumour staging to exclude distant metastasis before surgery. A board-certified radiologist conducted an independent blinded review in addition to the investigator review. Safety assessments were documented throughout the treatment period. Adverse events were graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.01). The frequency, duration, and severity of adverse events were recorded.

See Online for appendix

For biomarker assessment, AFP concentration and albumin-bilirubin score were measured at baseline, before stereotactic body radiotherapy, before avelumab initiation, every 2 weeks during the first 6 months of treatment with avelumab, and every 4 weeks thereafter. Exosomal PD-L1 concentration was measured at baseline, before stereotactic body radiotherapy, before avelumab initiation, and every 2 weeks in the first 3 months of treatment with avelumab. The methods are further detailed in the appendix (p 4).

Outcomes

The primary endpoint was the percentage of patients deemed to be amenable to curative treatment after conversion therapy. Amenability for curative treatment was fulfilled when one of the following criteria was met: either a sustained complete response or sustained partial response achieved for at least 2 months and if curative treatment could be performed (based on investigator's review). Curative treatment included R0 resection, if sufficient liver volume and function could be retained; radiofrequency ablation, which was reserved for patients with tumours downsized to less than 3 cm for whom resection was not feasible due to tumour location, or patients with tumours in a superficial location that could be safely dealt with by percutaneous ablation;[16] or transplantation, which was limited to patients with tumours downstaged to be within the University of California San Francisco criteria for liver transplantation that were deemed unsuitable for resection or ablation, who were 70 years or younger with cirrhosis complicated by portal hypertension.[17] The secondary endpoints were: objective response rate according to modified RECIST;

number of patients who became amenable and received curative treatment or achieved radiological complete response; progression-free survival, defined as time from TACE to first documented disease progression according to modified RECIST or death from any cause; time to progression, defined as time from TACE to first documented disease progression according to modified RECIST; overall survival, defined as time from TACE to date of death from any cause; quality-of-life measurement using the FACT-Hep score and EORTC QLQ-C30, measured every 3 months in the first year; toxicity as measured by the CTCAE (version 4.01) and Child–Pugh liver function score progression of two or more points;[18] pathological response, defined as the percentage of surface with non-viable cancer cells in relation to the total tumour area; disease control rate (DCR), expressed as the percentage of patients who had a complete response, partial response, or stable disease for at least 6 months; local control rate, defined as the percentage of lesions with absence of recurrence within the high-dose region (80% isodose volume); duration of response, defined as time from first documented evidence of complete response or partial response until the first documented disease progression or death from any cause; pattern of disease progression (in-field, out-field intrahepatic, new vascular invasion, or extrahepatic) per modified RECIST; and radiological response per RECIST (version 1.1). Post-hoc analyses included radiological response according to immune RECIST, correlation of clinical outcomes with BCLC stage, albumin-bilirubin score, radiological assessment criteria, biomarkers, and median time to treatment response.

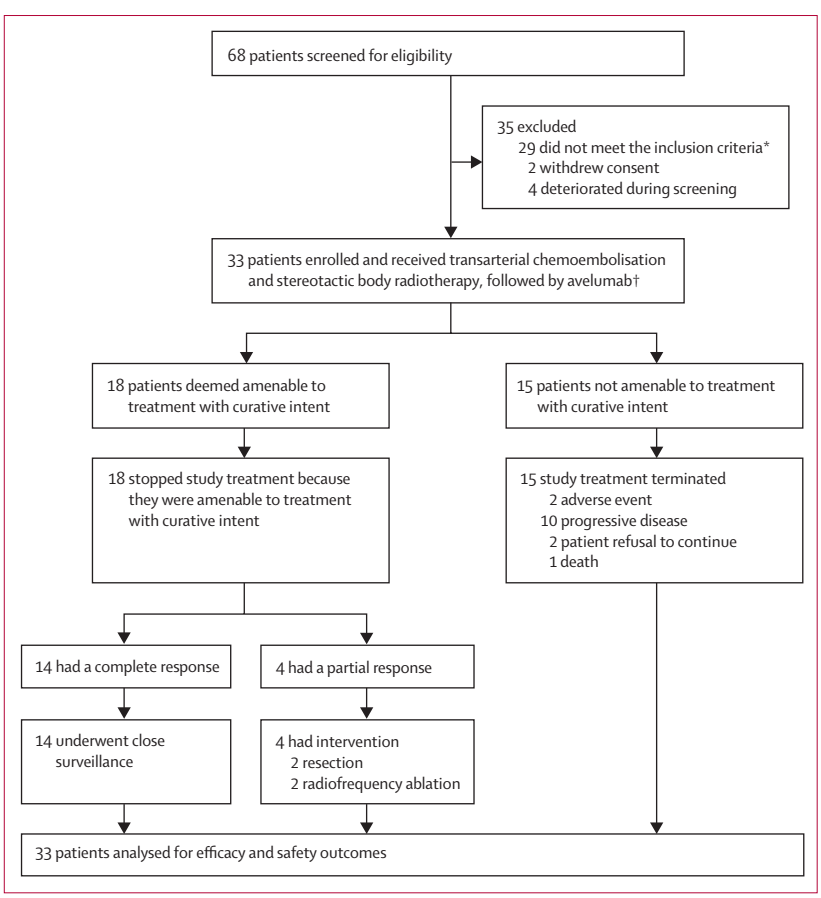


Figure 1: **Trial profile**
*29 patients were excluded for the following reasons: more than three lesions (n=11); extrahepatic vascular invasion (main portal vein thrombosis [Vp4] or inferior vena cava [VV3] involvement; n=5); extrahepatic metastases (n=4); poor liver function (n=2); liver volume minus gross tumour volume less than 700 mL (n=3); secondary malignancy (n=2); poor renal function (n=2). †One patient did not receive avelumab due to disease progression.

Statistical analysis

Our sample size was based on the assumption that approximately 20% of patients would be amenable to surgery with the START-FIT regimen, and that 5% of patients would be amenable to surgery with TACE only. These figures were extrapolated from historical institutional data. A modified Simon two-stage optimal design was used in view of its ability to minimise the expected number of patients under the null hypothesis, (80% power; level of significance, p=0·05; historical response rate, 5%; target response rate for treatment efficacy, 20%; stage 1 sample size of ten patients; total sample size of 29 patients, with an additional four patients to allow for dropout or other reasons).[19] In the first stage, ten patients were enrolled. If at least one patient could proceed to surgery, an additional 19 patients were recruited. If at least four of the total 29 patients could proceed to surgery, the treatment combination would be considered worthy of further investigation. Assuming a 10% loss to follow-up, a total of 33 patients would be recruited. All patients who received any study treatment were included in the intention-to-treat population and analysed for the primary and secondary outcomes, including the safety outcomes.

The percentage of patients deemed amenable to treatment with curative intent and the corresponding 95% CI were expressed as a binomial distribution. The objective response rate and corresponding 95% CI were estimated using the Clopper-Pearson method. The survival distributions were estimated using the Kaplan-Meier method for all the time-to-event endpoints and compared between subgroups (albumin-bilirubin and BCLC) by the log-rank test. The Brookmeyer and Crowley method estimated the median time to an event and corresponding 95% CI.[20] Comparison of exosomal PD-L1 concentrations among complete responders versus non-complete responders was conducted at baseline and 1 month after immunotherapy. For overall survival, data for patients who were not known to have died at the time of the analysis were censored at the last recorded date that the patient was known to be alive. For progression-free survival, data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of their last assessment (according to mRESIST) that could be evaluated.

	Patients (n=33)
Median age, years (range)	68 (62–74·5)
Sex	
Male	32 (97%)
Female	1 (3%)
Eastern Cooperative Oncology Group performance status	
0	26 (79%)
1	7 (21%)
Cause of liver cirrhosis	
Hepatitis B	24 (73%)
Hepatitis C	4 (12%)
Alcohol misuse	2 (6%)
Cryptogenic	3 (9%)
Child–Pugh score	
A5	23 (70%)
A6	9 (27%)
B7	1 (3%)
Albumin-bilirubin score	
Grade 1	21 (64%)
Grade 2	12 (36%)
BCLC stage*	
A	4 (12%)
B	8 (24%)
C without extrahepatic spread	21 (64%)
Reasons for cancer being unresectable	
Inadequate liver remnant volume, poor indocyanine green test result, or both	4 (12%)
BCLC stage B and beyond the up-to-7 criteria†	8 (24%)
BCLC stage C without extrahepatic spread	21 (64%)
Tumour vascular invasion	
No	12 (36%)
Yes	21 (64%)
Branched portal vein invasion	3 (9%)
Hepatic vein invasion	13 (39%)
Both portal vein and hepatic vein invasion	5 (15%)
Number of lesions	
One	17 (52%)
Two	12 (36%)
Three	4 (12%)
Median size of largest lesion, cm (IQR)	8·7 (6·2–12·7)
(Table 1 continues in next column)	
(Continued from previous column)	
Median sum of largest diameters of lesions, cm (IQR)	15·1 (8·3–14·9)
AFP, ng/mL	
≤400 ng/mL	27 (82%)
>400 ng/mL	6 (18%)
Previous treatment	
No	30 (91%)
Yes	3 (9%)
Resection	2 (6%)
Ablation	1 (3%)
Median gross tumour volume, mL (IQR)	345·4 (161·2–824·1)
Median planning target volume, mL (IQR)	474·9 (266·5–1113·5)
Median prescribed dose, Gy‡ (IQR)	30·0 (30·0–35·0)

Data are n (%) unless otherwise specified. BCLC=Barcelona Clinic Liver Cancer. *At time of registration. †Sum of the diameter of the largest tumour (cm) and the number of tumour greater than seven. ‡When multiple lesions were treated, some might have received a lower dose to meet the planning objectives.

Table 1: **Baseline demographic and tumour characteristics**

	Per investigator review	Per independent review
Objective response rate*	22 (67%, 48–82)	22 (67%, 48–82)
Complete response	14 (42%, 26–61)	14 (42%, 26–61)
Partial response	8 (24%, 11–42)	8 (24%, 11–42)
Suitable for treatment with curative intent	4 (12%, 3–28)	4 (12%, 3–28)
Unsuitable for treatment with curative intent	4 (12%, 3–28)	4 (12%, 3–28)
Stable disease	3 (9%, 2–24)	5 (15%, 5–32)
Progressive disease	8 (24%, 11–42)	6 (18%, 7–36)
Disease control rate†	23 (70%, 51–84)	24 (73%, 55–87)
Median duration of response, months (IQR)	20·2 (11·2–21·7)	20·2 (11·2–21·7)
Local control rate, % (95% CI)‡		
6 months	98% (94–100)	98% (94–100)
12 months	92% (84–100)	92% (84–100)
24 months	92% (84–100)	92% (84–100)

Data are n (%, 95% CI) of 33 patients, unless otherwise stated. RECIST=Response Evaluation Criteria in Solid Tumours. *Complete response or partial response. †Complete response, partial response, or stable disease for at least 6 months. ‡n=55 lesions.

Table 2: **Confirmed antitumour activity, evaluated by modified RECIST**

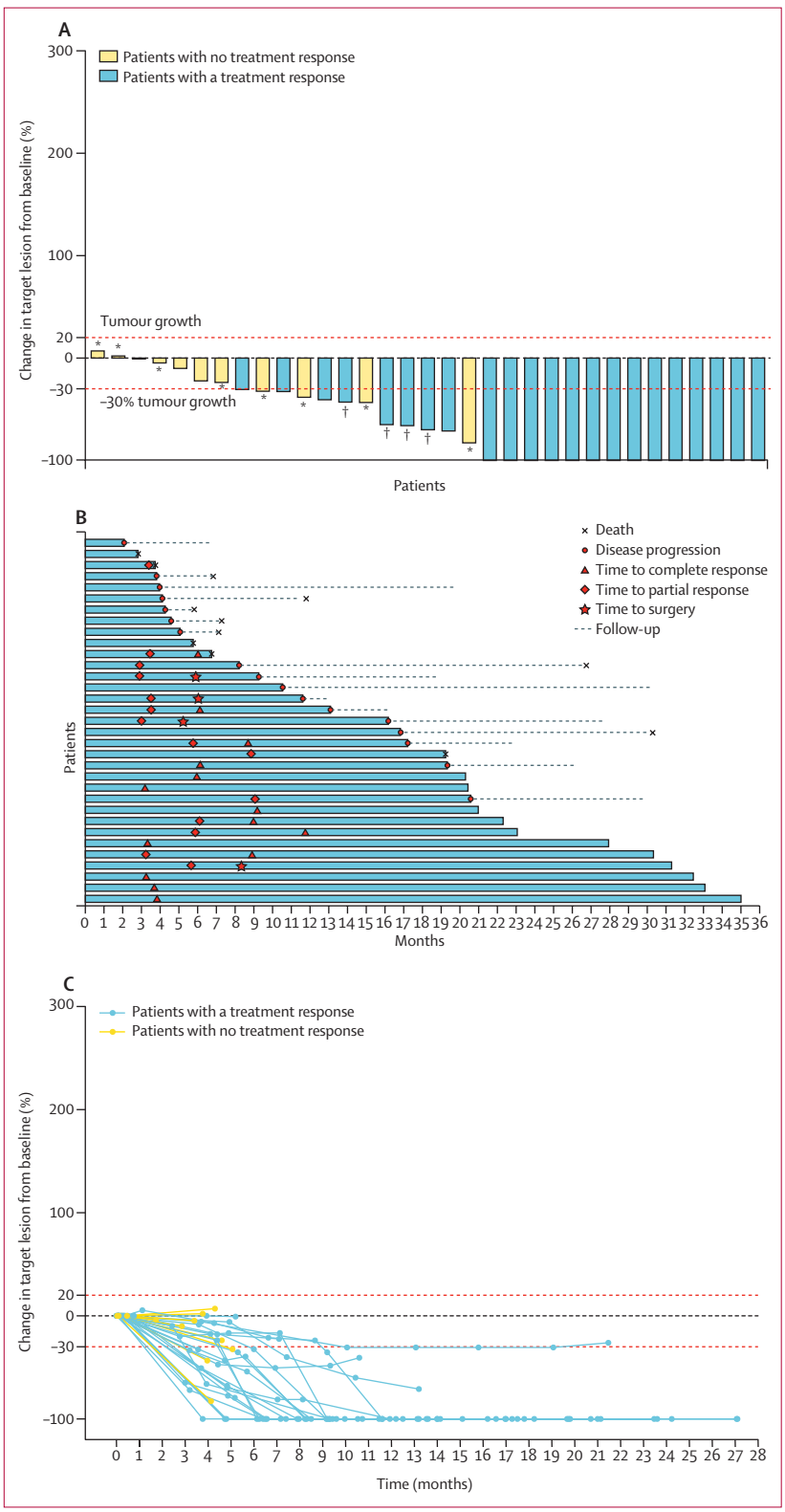
All quality of life scores were calculated using the EORTC and FACT-Hep methods, and the mean quality-of-life with 95% CI at each timepoint was tabulated. Analyses of outcomes between subgroups of patients with specific baseline categorical and continuous variables were conducted using a χ^2 distribution or a Mann–Whitney U test when appropriate. Statistical significance was defined as a p value of less than 0·05, and all the performed tests were two-tailed. Data were analysed using R (version 3.25). There was no data monitoring committee. This study is registered with ClinicalTrials.gov (NCT03817736).

Role of the funding source

The funders of this study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

Between March 18, 2019, and Jan 27, 2021, 68 patients were screened for eligibility. 29 patients did not meet the eligibility criteria (figure 1). However, four patients had



clinical deterioration before receiving the starting dose, and two patients withdrew consent (figure 1). Overall, 33 (49%) of 68 screened patients were deemed eligible and enrolled in the study. The baseline characteristics of the intention-to-treat population are detailed in table 1. Most of the patients recruited were male and had Child–Pugh class A. 21 (64%) patients had BCLC stage C disease with macrovascular invasion and eight had BCLC stage B disease and were beyond the up-to-7 criteria. The demographics and clinical characteristics of individual patients are presented in the appendix (pp 5–9).

At the time of data cutoff (Dec 31, 2021), all 33 patients had completed study treatment. Patients received a median of eight cycles (IQR 4·5–12·0) of avelumab. The median dose of stereotactic body radiotherapy was 30·0 Gy (range 30·0–35·0) in five fractions. 18 (55%) patients stopped study treatment because they were deemed amenable to treatment with curative intent. The remaining 15 (45%) patients were not deemed amenable to treatment with curative intent and discontinued study treatment for the following reasons: disease progression (n=10), adverse events (n=2), patient refusal (n=2), and death (n=1; figure 1). A summary of the stereotactic body radiotherapy dose parameters and subsequent treatment after disease progression are presented in the appendix (pp 10–11).

Of the 18 (55%) of 33 patients who were deemed amenable to curative treatment after receiving the START-FIT regimen, eight were deemed amenable to resection, nine were deemed amenable to radiofrequency ablation, and one was deemed amenable to liver transplantation (appendix pp 7–9). Among all 33 patients, 14 (42%) had a complete response and four (12%) had curative treatment (two patients had resection and two patients had radiofrequency ablation). Pathological review of the tumour specimens from the two patients who underwent resection showed a tumour necrosis rate that was 50% or higher. All patients who had a compete response opted for active surveillance (figure 1).

The confirmed objective response rate was 67% (95% CI 48–82), according to investigator review. The compete response rate was 42% (26–61), and the partial response rate was 24% (11–42; table 2). Three (9%) patients had stable disease, and eight (24%) patients had

Figure 2: **Tumour responses**
(A) Waterfall plot showing the percentage change from baseline in the sum of the longest diameter of target lesions in each of the 33 patients, according to treatment response per modified RECIST. (B) Swimmer plot showing the duration of response and time to response. Blue bar signifies duration of response. (C) Spider plot showing the percentage change from baseline in the sum of longest diameter of target lesions over time (months) in each of the 33 patients, according to treatment response per modified RECIST. RECIST=Response Evaluation Criteria in Solid Tumours. Dotted lines in A and C represent the definition of partial response and progressive disease per modified RECIST criteria. *Patients with a new lesion or lesions or progression of a non-target lesion. †Treated with curative intent.

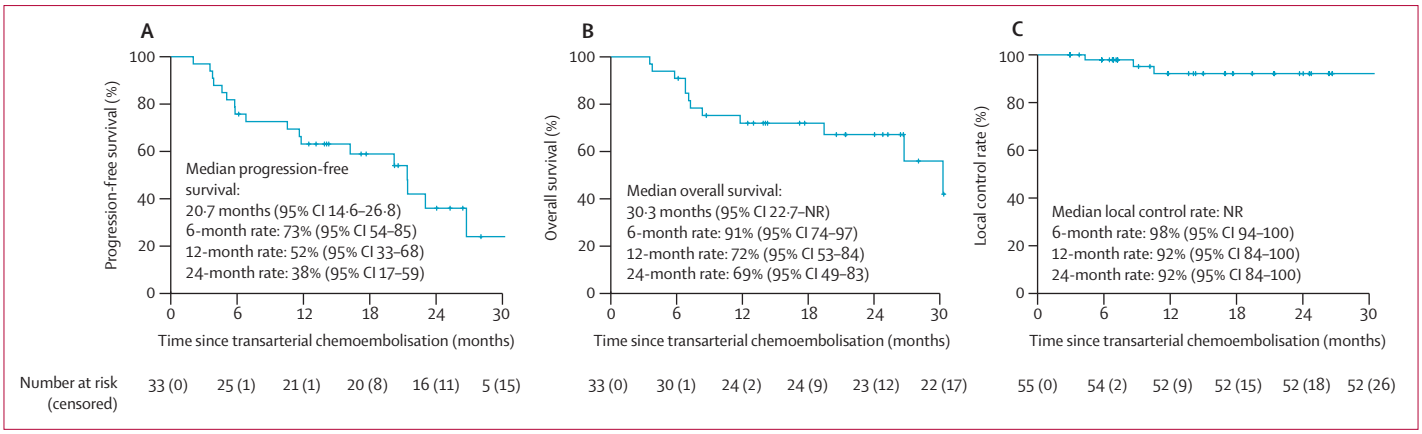


Figure 3: **Survival outcomes and local control**
(A) Progression-free survival, per patient (n=33). (B) Overall survival, per patient (n=33). (C) Local control, per lesion (n=55). NR=not reached.

progressive disease (table 2). The disease control rate was 70% (95% CI 51–84; table 2). According to independent review, the objective response rate was 67% (48–82) and the disease control rate was 73% (55–87; table 2). 31 (94%) of 33 patients had target lesions that showed tumour regression (figure 2A). Tumour responses as determined by RECIST (version 1.1) and immune RECIST are shown in the appendix (p 12).

The median time to treatment response was 3·8 months (95% CI 2·4–8·7). The median duration of response was 20·2 months (IQR 11·2–21·7). Notably, all 14 patients who had a complete response had stopped avelumab upon achieving a complete response. The median number of cycles of avelumab received among patients who had a complete response was nine (IQR 6·8–12·3). 11 (79%) of 14 patients who had a complete response did not have disease progression at the time of data cutoff after a median follow-up of 17·2 months (IQR 7·8–25·8; range 6·8–28·1; figure 2B). Changes in target lesions over time are presented in figure 2C. None of the patients relapsed within the radiation field (figures 2B, 2C).

After a median follow-up of 17·2 months (IQR 7·8–25·8; range 3·5–31·6) for the entire cohort, median progression-free survival was 20·7 months (95% CI 14·6–26·8), median time to progression was 21·4 months (16·4–26·4), and median overall survival was 30·3 months (22·7 to not reached; figures 3A, 3B). The 12-month local control rate (n=55 lesions) was 92% (95% CI 84–100) and the 24-month local control rate (n=55 lesions) was 92% (84–100; table 2; figure 3C). The 12-month progression-free survival rate was 52% (95% CI 33–68) and the 24-month progression-free survival rate was 38% (18–59; figure 3A). The 12-month overall survival rate was 72% (95% CI 53–84) and the 24-month overall survival rate was 69% (49–83; figure 3B). The 24-month overall survival rate of patients amenable to surgery (n=18) was 94% (79–100). Among them, the 24-month overall survival rate of patients who had a complete response and opted for close surveillance (n=14) was 92% (78·5–100·0) and the 24-month overall survival of patients who underwent curative treatment (n=4) was 100% (94·2–100·0). The causes of death among the 12 patient events recorded included disease progression (n=6), decompensated liver failure (n=2), medical illness (n=2), suicide (n=1), and accident (n=1; figure 1). Of the 17 patients who eventually developed disease progression, 13 (77%) presented with intrahepatic out-of-field progression (appendix p 14).

Treatment-related adverse events occurred in all patients during the study treatment period (table 3). 11 (33%) of 33 patients had at least one treatment-related adverse event that was grade 3 or worse. The most common treatment-related adverse events that were grade 3 or worse were increased alanine aminotransferase or aspartate aminotransferase (five [15%] of 33 patients; table 3), increased bilirubin (two [6%]), and an increase in both alanine aminotransferase or aspartate aminotransferase and bilirubin (two [6%]) after TACE. All seven (21%) patients with treatment-related hepatic impairment recovered uneventfully and were managed conservatively. The most common immune-related adverse events of grade 3 or worse, which occurred in five (15%) of 33 patients, were hepatitis and dermatitis (table 3). All patients with immune-related adverse events responded to steroid treatment (oral prednisolone 1 mg/kg). However, treatment with avelumab was permanently discontinued in two patients due to immune-related adverse events. Temporary dose interruption of avelumab occurred in seven (21%) patients with a median duration of interruption of 4 weeks (IQR 2–5; range 1–8).

Treatment-related adverse events related to TACE, stereotactic body radiotherapy, and avelumab are presented separately in the appendix (pp 15–18). No radiation-induced liver disease or treatment-related deaths were observed. Child–Pugh score deterioration of at least 2 points was detected in three (12%) of 25 patients

	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse events	27 (82%)	3 (9%)	8 (24%)	0
Lead to discontinuation	0	1 (3%)	1 (3%)	0
Constitutional				
Fatigue	21 (64%)	0	0	0
Fever	10 (30%)	0	0	0
Infusion-related reaction	7 (21%)	0	0	0
Weight decreased	7 (21%)	0	0	0
Ascites	5 (15%)	1 (3%)	0	0
Weight gained; dizziness; hoarseness	11 (33%)	1 (3%)	1 (3%)	0
Skin				
Rash, maculopapular	10 (30%)	1 (3%)	0	0
Rash, acneiform	3 (9%)	0	0	0
Rash, urticarial	3 (9%)	1 (3%)	0	0
Herpes zoster	3 (9%)	0	0	0
Pruritus	8 (24%)	1 (3%)	0	0
Dry skin	11 (33%)	1 (3%)	0	0
Bilateral lower extremity oedema	1 (3%)	0	0	0
Gastrointestinal				
Decreased appetite	9 (27%)	0	0	0
Nausea	14 (42%)	1 (3%)	0	0
Vomiting	7 (21%)	0	0	0
Diarrhoea	4 (12%)	0	0	0
Stomatitis	4 (12%)	0	0	0
Constipation	5 (15%)	0	0	0
Gastritis or gastrointestinal bleed	1 (3%)	0	0	0
Others	6 (18%)	0	0	0
Hepatic				
Abdominal pain	7 (21%)	0	0	0
Alanine aminotransferase increased	13 (39%)	5 (15%)	1 (3%)	0
Aspartate aminotransferase increased	16 (48%)	1 (3%)	6 (18%)	0
Gamma-glutamyl transferase increased	2 (6%)	1 (3%)	0	0
Bilirubin increased	24 (73%)	2 (6%)	0	0
Alkaline phosphatase increased	19 (58%)	1 (3%)	0	0
Laboratory				
Anaemia	19 (58%)	0	0	0
Leukopenia	14 (42%)	0	0	0
Neutropenia	2 (6%)	0	0	0
Thrombocytopenia	10 (30%)	0	0	0
Hyperglycaemia	1 (3%)	0	0	0
Hyponatraemia	13 (39%)	0	1 (3%)	0
Hypokalaemia	7 (21%)	0	0	0
Hypercreatinine	3 (9%)	0	0	0
Hypothyroidism	5 (15%)	0	0	0
Immune-related				
Hepatitis	2 (6%)	3 (9%)	0	0
Dermatitis	2 (6%)	2 (6%)	0	0
Other immune-related events*	5 (15%)	0	0	0

Data are n (%) of 33 patients. *Hypothyroidism; adrenal insufficiency.

Table 3: **Treatment-related adverse events**

at 3 months, in three (14%) of 22 patients at 6 months, and in one (6%) of 17 patients at 12 months after enrolment. There was no significant deterioration in quality-of-life scores throughout the study period (appendix pp 25–26).

Decreasing serum AFP concentrations were observed in most patients (28 [84·4%] of 33) enrolled in the study (appendix p 27). However, there was no correlation between serum AFP changes over time and radiological responses. Median progression-free survival was 22·2 months (95% CI 18·4–27·6) in the 21 patients with albumin-bilirubin grade 1 and 6·8 months (95% CI 0–14·8) in the 12 patients with albumin-bilirubin grade 2 (p=0·070). Although there were numerical differences in overall survival, objective response rate, and disease control rate between the two albumin-bilirubin grades, these differences were not statistically significant (appendix pp 19, 28–29). Dynamic changes in exosomal PD-L1 concentrations were evaluated in 24 patients. Patients who had a surge of exosomal PD-L1 at week 8 of avelumab (to 250 pg/mL or higher) had a better complete response rate than those who had exosomal PD-L1 concentrations lower than 250 pg/mL (10 [63%, 95% CI 39–82] of 16 patients with PD-L1 ≥250 pg/mL had a complete response *vs* 2 [25%, 95% CI 9–53] of 8 with PD-L1 <250 pg/mL; p=0·049; appendix p 30). The median progression-free survival of patients with BCLC stage A and B beyond the up-to-7 criteria (n=12) was 26·7 months (95% CI 18·5–35·0) compared with 11·8 months (0–27·2) for patients (n=21) with BCLC stage C (p=0·070). The 24-month overall survival rate among patients without macrovascular invasion was 91% (82–100) compared with 57% (33–80) among patients with macrovascular invasion (p=0·23). Ten (83%) of 12 patients with BCLC stage A and B beyond the up-to-7 criteria became amenable to surgery compared with eight (38%) of 21 patients with BCLC stage C (p=0·012; appendix pp 13, 23–24). Notably, more patients with albumin-bilirubin grade 2 had a Child–Pugh score progression of at least 2 points than did those with albumin-bilirubin grade 1 (appendix p 19).

Discussion

In this trial, sequential TACE, stereotactic body radiotherapy, followed by PD-L1 blockade in patients with locally advanced unresectable hepatocellular carcinoma resulted in 55% of patients becoming amenable to curative treatment, and 12% of patients undergoing curative treatment. Moreover, 42% of patients who were enrolled in the trial had radiological complete response without surgery, and a 2-year overall survival rate of 92%. To our knowledge, this was the first prospective clinical trial using sequential locoregional treatment combined with immunotherapy as conversion therapy for locally advanced unresectable hepatocellular carcinoma. The objective response rate of 67% is promising compared with that of standalone systemic

therapy (14–40%) and TACE (30%) in similar patient populations.[4–6] Over 60% of our cohort had BCLC stage C disease, representing a spectrum of hepatocellular carcinoma characterised by poor prognostic outcomes due to macrovascular invasion. According to current international guidelines, these patients are not candidates for locoregional therapies, and systemic therapy remains the standard of care.[21] In line with our study findings, studies from 2021[22] and 2022[23] showed that multimodality treatment might induce a more profound and durable tumour response in patients with advanced hepatocellular carcinoma.

An individualised stereotactic body radiotherapy dose-allocation strategy was adopted to treat large, multi-foxpatocellular carcinoma with macrovascular invasion.[7,24] A drawback of this approach is that sizable lesions are more likely to receive non-ablative doses, and the radiation doses prescribed are heterogeneous.[7,24] Our patients received radiation for all gross lesions; emerging evidence favoured the comprehensive radiation of all tumour sites to improve immune access and reduce the immunosuppressive effects of bulky lesions.[25] Our favourable local control and complete response rates could be explained by the additive effect of TACE, radiotherapy, iodised oil staining to improve tumour target localisation,[26] and most importantly, the synergistic immunomodulatory effect of the combined regimen.[8–12,26] Preclinical data suggested that immune checkpoint inhibitors could sensitise the tumour to radiotherapy and that lower radiation doses can attain similar local control.[27] The possibility of using lower radiation doses is particularly important when treating large hepatocellular carcinomas with stereotactic body radiotherapy, because the radiation dose permitted is often limited by the tolerance of normal liver parenchyma. However, adding immunotherapy could reduce the chance of out-of-field progression after locoregional therapy. Indeed, the immunomodulatory effect of TACE and stereotactic body radiotherapy might further augment the effect of immune checkpoint inhibitors in eradicating occult metastasis.[28]

Our trial required that patients had a sustained response after the tri-modality therapy and were suitable for surgery to reach the primary endpoint. A multidisciplinary board evaluated all patients to determine the feasibility and type of curative treatment. The primary endpoint of the trial encompassed different modalities of curative treatment, reflecting the real-world practice in all attempts to improve survival outcomes of patients with advanced hepatocellular carcinoma. However, the diversity of curative treatment options used in the START-FIT trial, including transplantation, might have introduced selection bias that could undermine the validity of our findings, although the number of patients deemed eligible for transplantation was small.

The safety profile of the triple therapy regimen was consistent with the safety profile previously observed with TACE, stereotactic body radiotherapy, or avelumab alone.[6] All seven patients who developed a transient impairment of liver function that was grade 3 or worse due to TACE continued stereotactic body radiotherapy without delay. We showed that, in terms of preventing Child–Pugh class deterioration, the START-FIT regimen compared favourably with repeated TACE.[29]

There were some study limitations that merit further discussion. The was a single-arm study; therefore, the additive effect of avelumab on locoregional therapy remains unclear. Treatment strategies in hepatocellular carcinoma continue to evolve; however, the optimal response assessment criteria in patients receiving combination therapy remain undefined.[30] We used modified RECIST, RECIST (version 1.1), and immune RECIST to assess treatment responses to address this issue, and the modified RECIST better correlated with patient survival. Furthermore, over 70% of our study cohort had chronic hepatitis B, so the findings from our study might not be easily adopted in patient populations with different causes of disease. Moreover, three patients with recurrent hepatocellular carcinoma who relapsed after primary treatment were included in the efficacy analysis. These patients might have a different disease course than treatment naive patients. The low proportion of female patient participation might also affect the generalisability of our findings to this patient population.

In conclusion, the START-FIT regimen could be a promising conversion therapy for patients with locally advanced unresectable hepatocellular carcinoma. This strategy might represent a new opportunity for onco-surgical downstaging; however, further investigation, including randomised trials, is required before adoption of this approach .

Contributors

CLC and AC conceived and designed the study. CLC, AC, KWHC, FASL, WCD, TCL, WQC, NSMW, and VWHL contributed to patient recruitment and provision of study materials. CLC, AC, KWHC, CWSW, and JCBL collected and assembled the data. KSKC performed data analysis. CLC, AC, and KWHC interpreted the data. All authors confirmed that they had full access to, and verified, all the data in the study, and contributed to the writing and approval of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual patient data will not be available. The study protocol is available on request to acchan@hku.hk.

Acknowledgments

This study was financially supported by Merck, an affiliate of Merck KGaA (CrossRef Funder ID: 10.13039/100009945), as part of an alliance between Merck and Pfizer. We thank the patients who participated in the trial. We appreciate the efforts of John K S Fong, Yuuki T Y Tam, and Crystal L Y Kwan for data collection and assembly.

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